

REMARKS

Claims 1-15, 17-34, 36-45 and 48-66 were pending. Claims 5-8 and 51-62 were withdrawn as drawn to non-elected subject matter. Claims 2-4, 9, 11 and 12 are canceled herein without prejudice or disclaimer. Applicant reserves the right to prosecute the canceled subject matter in a continuation or divisional application. No new claims have been added. Claims 1, 10, 13-15, 17-34, 36-45, 48-50 and 63-66 are presently under examination. Claims 1, 10, 13, 25, 26, 30, 32, 44 and 45 are amended. Applicant submits that no new matter is added by the amendment.

Claims 25, 26, 44 and 45 are amended to correct typographical errors.

Claim 1 is amended to include the elements previously recited in claims 2-4 which depended from claim 1 and are now canceled. Claim 1 is amended to clarify that the thiol group is on the antibody and not on the chemotherapeutic moiety. Support for the amendment may be found in the published Specification (No. 20040185053) at least in original claims 2-4, 9, 10, and Paragraphs [0015], [0033], [0047], [0048] and Example 8.

Claim 10 is amended to avoid dependence from a canceled claim and to conform antecedent basis support with the language of claim 1. Claim 13 is also amended to avoid dependence from a canceled claim.

Claim 30 has been amended to clarify the claimed subject matter to include the limitation "a peptide comprising." Support for this amendment can be found in the specification, at least at paragraph [0080] of the published application.

Claim 32 has been amended to clarify the claimed subject matter. Support for this amendment can be found in the specification, at least at paragraphs [0045] and [0046] of the published application.

Claim Rejections - 35 USC § 112, first paragraph

The Action rejected claims 25-26, 44, 46-47 and 63-66 for failure to comply with the enablement requirement, because "the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description." [Action at pg. 3, 1st paragraph] The Action further states that, "As required elements [the antibodies] must be known and readily available to the public or obtainable by a

repeatable method set forth in the specification, or otherwise readily available to the public.”

[Action at pg. 3, 2nd paragraph]

The Action at pg. 4, last paragraph states, “the Examiner acknowledges that the antibodies were known prior to the effective filing date of the instant application. However, the Examiner recognizes that the instant situation is amendable to the type of analysis set forth in *Ex parte Humphreys*, 24 USPQ2d 1255 (Bd. Pat. App. & Int. 1992), wherein the court held that the only manner in which applicants could satisfy their burden of assuring public access to the needed biological material, and, thereby, compliance with the enablement requirement of 35 U.S.C. 112, was by making an appropriate deposit.”

Applicant respectfully submits that the reliance of the Patent Office on *Ex parte Humphreys* to reject claims drawn to monoclonal antibodies of known sequence is misplaced. In the *Humphreys* case, the biological material in question concerned a plasmid pIJ2303, comprising certain nucleic acid sequences useful as probes to isolate related genes. The Board of Patent Appeals and Interferences stated that,

Appellants have also traced the manner in which pIJ2303 was developed as documented in the prior art. See the paragraph bridging pages 3-4 of the Reply Brief, relying upon, *inter alia*, *Hopwood I*. As explained by appellants, the genesis of this plasmid can be traced to ultraviolet mutagenesis of certain bacterium. Appellants assert that mutagenesis is a well-known and reproducible technique so that pIJ2303 can be reconstructed by those skilled in this art if the plasmid is not publicly available. Appellants also refer to disclosures in other references, e.g., *Malpartida* 1984, that the mutant strains from which pIJ2303 was developed are maintained at the John Innes Institute so that it may be implied that these mutant strains are available to researchers interested in reconstructing this plasmid. [*Ex parte Humphreys*, 24 USPQ2d 1255 (Bd. Pat. App. & Int. 1992)]

In maintaining the Examiner’s rejection, the Board concluded that,

In regard to reconstructing pIJ2303, we point out that appellants have not provided any evidence on this record that ultraviolet mutagenesis of bacteria is a reproducible phenomenon so that the mutant bacteria needed in order to reconstruct pIJ2303 may be obtained without undue experimentation. [*Id.*]

In contrast, in the instant case there is no requirement for mutagenesis to produce the recited antibodies. The sequences of the antibody variable regions were known in the art as of the instant priority date, as summarized in the amendment and response dated November 16, 2006. The antibodies recited in the instant claims are not mutagenized from the known sequences. There is

therefore no requirement for undue experimentation in producing antibodies comprising such known sequences.

The Appellants in *Humphreys* further asserted that the nucleotide sequence of one of the claimed genes was publicly known. The Board concluded that,

In response to appellants' reliance upon the later published Hallam reference for its disclosure of the nucleotide sequence of one of the genes involved in the present invention, the examiner argues that such a later published reference is not available for appellants' use to establish enablement, citing *In re Glass*, 492 F.2d 1228, 181 USPQ 31 (CCPA 1974). Appellants respond that under the circumstances of this application, the later published reference may be relied upon in this manner, citing *In re Lundak*, 723 F.2d 1216, 227 USPQ 90 (Fed.Cir.1985). We do not find it necessary to resolve this specific issue since, assuming arguendo, Hallam is properly relied upon by appellants, we do not find that it relieves appellants of their burden of depositing pJ2303.

At best, Hallam discloses the nucleotide sequence of a single gene involved in the present invention. Appellants have not explained on this record how this disclosure in and of itself enables practice of the present invention throughout the breadth of the rejected claims. Appellants direct attention to dependent claims 4 and 12 which are stated to be limited to the use of the subsequently published nucleotide sequence. We disagree. These claims only require the use of "the nucleic acid sequence of at least a part of the actinorhodin gene III" and are not limited to the use of the subsequently published nucleotide sequence as argued. [*Id.*]

Again, the facts in *Humphreys* are simply not analogous to the instant application. In *Humphreys*, multiple genes were required for the practice of the claimed method, and only one had been previously disclosed. In the instant application, the sequences of the antibodies in question were publicly disclosed before the instant priority date.

While Applicant traverses the requirement for a deposit, in the interests of advancing prosecution, at least the deposits of hybridomas encoding antibodies LL2 (ATCC PTA-6735), G250 (2526), CC49 (ATCC HB 9459, HB 12127 and HB 12126) and L243 (ATCC HB55), as discussed in the response and amendment of November 16, 2006, were made under the terms of the Budapest Treaty and all restrictions imposed by the depositor will be irrevocably removed upon the granting of a patent.

For the reasons discussed above, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Claim Rejections - 35 USC §103

Rejections over Chari

Claims 1-4, 9, 11-15, 17, 19, 21-24, 27-31, 33-34, 36, 38, 40-43 and 48-50 were rejected under 35 U.S.C. 103(a) as being unpatentable over Chari (WO 01/24763, 2001) in view of Zhao (US 6,716,821, 2004).

Claims 25 and 44 were rejected under 35 U.S.C. 103(a) as being unpatentable over Chari in view of Zhao in further view of Newton (Blood 2001; 97: 528-535).

Claims 18, 20, 26, 37, 39, 45 and 47 were rejected under 35 U.S.C. 103(a) as being unpatentable over Chari in view of Zhao and Newton in further view of Cao (Bioconjugate Chemistry 1998; 9: 635-643). The Action states on page 10 that the Applicant's arguments have been found persuasive with respect to the rejection of these claims. Applicant thanks the Examiner for the withdrawal of this rejection.

Applicant has canceled the claims 2-4, 9, 11 and 12 and have amended independent claim 1 from which the rest of the claims depend. Applicant submits that amended claim 1 is not obvious over the prior art. Since the rest of the claims 9, 10, 13-15, 17, 19, 21-25, 27-31, 33, 34, 36, 38, 40-44 and 48-50 contain all of the elements of claim 1 plus additional elements, the Applicant submits that these claims are also not obvious over the prior art.

A prima facie case of obviousness requires: (1) a teaching or suggestion of all of the claim limitations; (2) a suggestion or motivation to modify or combine the teachings of the applied prior art; and (3) a reasonable expectation of success in reaching the claimed invention. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. [MPEP 2142, citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).] Applicant submits that each of those requirements is lacking here.

Amended claim 1 recites, "An immunoconjugate comprising: (a) an antibody; (b) a chemotherapeutic moiety; and (c) a linker comprising (i) a thiol-reactive functional group that binds to a thiol group on the antibody, and (ii) a water-solubilizing moiety, wherein the chemotherapeutic moiety is attached to the linker via an intracellularly-cleavable moiety that is

cleavable by intracellular esterases and comprises an ester formed from the α -carboxylic acid of an amino acid."

Neither Chari nor Zhao, either alone or in combination, disclose all elements of the amended claims. First, the element of "a linker comprising a thiol-reactive functional group that binds to a thiol group on the antibody" is not disclosed. The Action, on page 11, acknowledges that Zhao does not teach that the linker comprises a thiol-reactive functional group for binding to the antibody, but contends that this limitation is clearly taught by Chari. Applicant respectfully disagrees. In instant claim 1, the binding between the linker and the antibody occurs via a *thiol reactive functional group on the linker*, which binds to a *thiol group on the antibody*. In Chari the orientation of the bond is reversed and the thiol reactive group is on the antibody. Furthermore, in Chari the bond occurs between the antibody and a thiol-containing anti-mitotic drug. [Chari pg. 20-22] The use of a thiol containing drug for antibody conjugation has the disadvantage of possible cleavage of disulfide bonds within the antibody that are important for maintaining the antibody structure. Another disadvantage is that thiol-containing agents can form aggregates, removal of which requires an additional step of HPLC purification. [Chari at pg. 20, line 6] The instant disclosure of conjugation of the antibody via a bond between a thiol group on the antibody and a thiol reactive group on the linker solves both of these problems. Thus, the element of "a linker comprising a thiol-reactive functional group that binds to a thiol group on the antibody" is not disclosed in Chari and/or Zhao.

Second, amended claim 1 recites that the chemotherapeutic moiety is attached via an intracellularly-cleavable moiety that is cleavable by intracellular esterases and comprises an ester moiety formed from the α -carboxylic acid of an amino acid. Thus, the ester bond in the instant invention is between the chemotherapeutic moiety and a *natural* α -amino acid. In contrast, in Chari the ester bond is between the antimetabolic drug and carboxylic acid derivatives that *are not naturally occurring amino acids*. [Chari, pg. 6-7] Thus, this element is also not disclosed in Chari and/or Zhao.

Finally, MPEP section 2143.03 states that the prior art must be viewed in its entirety by considering not only that section which may have similarity to the claimed invention, but also the section that teaches away from the claimed invention. Applicant points out that the disclosure of Chari is fundamentally different from the instant claimed subject matter. Chari discloses a

combination therapy using an immunoconjugate and, separately, a therapeutic agent. The instant claims recite an antibody linked to a chemotherapeutic agent (via a linker group) to form an immunoconjugate. Thus, Chari's disclosure of a combination therapy in which the chemotherapeutic agent is administered separately from the immunoconjugate teaches away from the instant invention.

With respect to the reference of Newton, that reference is cited by the Action as merely disclosing, "an immunoconjugate comprising LL2 covalently linked to the ribonuclease, onconase, wherein LL2 is an anti-CD22 monoclonal antibody against B-cell lymphoma." [Action at pg. 8, 2nd to last paragraph] There is no citation to Newton as disclosing anything relating to "a linker comprising (i) a thiol-reactive functional group that binds to a thiol group on the antibody, and (ii) a water-solubilizing moiety, wherein the chemotherapeutic moiety is attached to the linker via an intracellularly-cleavable moiety that is cleavable by intracellular esterases and comprises an ester formed from the α -carboxylic acid of an amino acid," elements of amended claim 1.

Thus, none of the references, either alone or in combination, teach or suggest all of the claim limitations, nor do they contain a suggestion or motivation to modify or combine their teachings to achieve the claimed compositions. Based upon these references an ordinary artisan would have no reasonable expectation of success in reaching the claimed compositions. Therefore, Applicant respectfully submits that claim 1 is not obvious over the cited prior art. Since the other claims all depend from claim 1, and contain additional elements, Applicant respectfully submits that these claims are also not obvious.

Rejections over Firestone

Claims 1-4, 9-15, 17-24, 27, 29-43, 48 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Firestone (US 6,214,345) in view of Greenwald (US 5,824,701) and Miller (224th ACS National Meeting, Boston, Mass., Poster Presentation). Claims 25-26, 44-45 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Firestone in view of Greenwald and Miller in further view of Newton. Applicant respectfully traverses the rejections.

Firestone is cited as teaching a drug ligand conjugate and a peptide linker. Greenwald is cited as teaching "taxane prodrugs having a water soluble PEG derivative," Miller as teaching

“development of Taxoid derivatives with enhanced toxicity and solubility,” and Newton as teaching “an immunoconjugate comprising [the antibody] LL2.” Applicant respectfully points out that none of these references disclose all the elements of the amended claims. Specifically, none of the cited prior art, alone or in combination, teach or suggest, “a linker comprising (i) a thiol-reactive functional group that binds to a thiol group on the antibody, and (ii) a water-solubilizing moiety, wherein the chemotherapeutic moiety is attached to the linker via an intracellularly-cleavable moiety that is cleavable by intracellular esterases and comprises an ester formed from the α -carboxylic acid of an amino acid,” as recited in amended claim 1.

In Firestone the bond between the drug and the peptide linker is within the peptide segment, and is cleavable by *proteases*. [Firestone, at column 4, lines 45-52] In contrast, in the instant claim 1, the attachment of the chemotherapeutic agent occurs through an ester bond which is cleavable by intracellular *esterases*. Because of this difference, the conjugate of the instant invention has an advantage over the Firestone conjugate. In Firestone the liberation of the drug from the conjugate can only occur in the lysosome and is dependent upon the expression levels of lysosomal proteases, whereas in the instant claims the ester bond can be hydrolyzed by esterases in either lysosome and cytoplasm, independent of the expression levels of lysosomal esterase enzymes, leading to more efficient release of the chemotherapeutic agent.

Additionally, Firestone discloses a drug ligand conjugate in which a drug, a self-immolating spacer, a protein peptide moiety, and a ligand binding moiety are all arranged in a *linear* configuration. [Firestone Column 3, lines 19-36] In contrast, in the instant claims 29 and 30, the drug attachment is *orthogonal* to the peptide linker, as the chemotherapeutic moiety is attached to the side chains of the amino acids of the peptide linker. Thus, it is possible to attach multiple chemotherapeutic agents to the amino acid side chains of a single peptide linker, whereas in Firestone only one drug molecule can be attached to the linker due to the linear configuration.

The Action’s assertion that Firestone, “teaches that the conjugate is susceptible to enzymatic cleavage at the bond covalently linking the spacer moiety and the protein peptide moiety, wherein the bond may be an ester bond and the ester is formed from the α -carboxylic acid of an amino acid (column 5, lines 5-10 and conjugates of Formula I),” is not understood. Col. 5, lines 5-10 merely recite, “a tripartate molecule with is stable and pharmacologically inactive in the absence of the target enzyme, but which is enzymatically cleavable by such target enzyme at

the bond covalently linking the spacer moiety and the protein peptide moiety to thereby effect release of the protein peptide moiety from the tripartite molecule.” There is no mention in the cited passage to cleavage by intracellular esterases, and in any case amended claim 1 refers to an ester linkage attaching the *chemotherapeutic moiety* to the linker, not a protein peptide moiety to a spacer moiety.

Thus, the conjugate disclosed in Firestone is distinct from the immunoconjugate of the instant claims, and Firestone fails to disclose all elements of the amended claims. The deficiencies of Firestone are not corrected by Greenwald, Miller and/or Newton, none of which contain any disclosure relevant to the element in claim 1 of a linker attached to a chemotherapeutic moiety via “an intracellularly-cleavable moiety that is cleavable by intracellular *esterases* and comprises an ester formed from the α -carboxylic acid of an amino acid.” (emphasis added)

As the cited prior art, alone or in combination, fails to disclose all elements of amended claim 1, a prima facie case of obviousness has not been established. Since the other rejected claims depend from claim 1 and therefore also include the missing elements, a prima facie case of obviousness has also not been established for the dependent claims.

For the reasons discussed above, Applicant respectfully submits that a prima facie case of obviousness has not been established for the amended claims. Therefore, rejection of the amended claims under 35 U.S.C. 103 is improper. Reconsideration and withdrawal of the rejection is requested.

Double Patenting

Claims 1-4, 9-15, 17-34 and 36-50 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-41 and 47-62 of co-pending application No. 11/388,032. The Action acknowledges Applicant's request in the previous response that the provisional double patenting be held in abeyance until such time as allowable subject matter is indicated in one of the two applications.

Conclusion

In conclusion, all of the claims remaining in this application should now be seen to be in condition for allowance. A prompt notice to that effect is respectfully solicited. If there are any remaining questions, the Examiner is requested to contact the undersigned at the number listed below.

Respectfully submitted,

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